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Original Article

Pathology Section

Prognostic Importance of Red Cell Distribution Width, Mean Platelet Volume and Neutrophil Lymphocyte Ratio among Sepsis Patients at a Tertiary Setting in Kolar, South India

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ABSTRACT

Introduction: Complete Blood Count (CBC) analysis contain several parameters that are routinely investigated during admission. Of these parameters, Red-Cell Distribution Width (RDW), Mean Platelet Volume (MPV), Neutrophil-Lymphocyte Ratio (NLR) have been observed as independent risk factors for various systemic diseases.

Aim: To compare the prognostic value of RDW, MPV, NLR with Sequential Organ Failure Assessment (SOFA) score among sepsis survivors and non survivors.

Materials and Methods: A prospective observational study was conducted among 120 sepsis patients admitted in department of General Medicine and Intensive Care Unit (ICU) at a tertiary care and research center in Kolar, South India, for 18 months from January 2018 to July 2019. Patients information regarding age, gender, SOFA scores, and parameters like RDW, MPV, NLR were recorded from the blood sample. The SOFA score, RDW, NLR, and MPV levels were considered explanatory variables for sepsis patients' mortality. To test significance, independent t-test and Chi-square test were used. Correlation analysis was performed with the pearson correlation coefficient. The SOFA score, RDW, MPV, and NLR were further analysed using the receiver operating characteristic (ROC). The level of significance was set at ≤0.05. coGuide software, V.1. was used for data analysis.

Results: All 120 subjects were divided into two groups. Survivor's group had 79 (65.8%) subjects, and 41 (34%) were in non-survivor's groups. Most of the survivors were in the age group 60-79 years which were 29 (36.71%), whereas non survivors were 40-59 years which were 17 (41.46%). Maximum were males in both the groups. Fever was the most common presenting symptom in survivors, 62 (78.48%) and non survivors 31 (75.61%). The calculated Area Under Curve (AUC) for RDW was 0.973 with 90.24% sensitivity and 97.47% specificity. The AUC for MPV was 0.966 with 92.68% sensitivity and 97.47% specificity, and for NLR, it was 0.984 with 100% sensitivity and 89.87% specificity. The yielded AUC for SOFA score was 0.772 with 56.10% sensitivity and 89.87% specificity. Ventilator and ionotropic support were strongly associated between groups (p-value <0.001). There was a significant difference among survivors and non survivors for SOFA score (p-value <0.001), systolic and diastolic blood pressure, pulse rate, GCS, and investigations like RDW, NLR, and MPV (p-value <0.001).

Conclusion: This study demonstrated a strong correlation between increased levels of RDW, NLR, MPV and mortality among sepsis patients and can be used as prognostic markers for mortality prediction in adult sepsis patients.

Keywords: Biomarkers, Complete blood analysis, Inflammatory marker, Systemic inflammation, Ventilation

INTRODUCTION

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. It is usually manifested as systemic inflammatory response syndrome (SIRS) to the causative infection. Worldwide, there is an increase in incidence of sepsis and septic shock [1]. Sepsis has become a life-threatening burden to public health, due to increased mortality in intensive care units [2]. In 2017, approximately 11.0 million deaths were reported globally, and in the past few years, there has been a decreasing trend in incidence and mortality due to sepsis [3]. Systemic inflammation, tissue hypoperfusion, organ dysfunction, and immune disorder are common manifestations of sepsis due to infections [4].

Pathogenesis of sepsis includes tissues, cell types, organ systems, and many inflammatory mediators, involving release of many biomarkers, that suggests role of biomarkers in sepsis management. Nearly 180 molecules were proposed as sepsis biomarkers [5]. These physiological changes influence Complete Blood Count (CBC). Red cell distribution width (RDW), Mean Platelet Volume (MPV), and Neutrophil-Lymphocyte Ratio (NLR) are parameters obtained from routine CBC [6].

For diagnosing sepsis, complete blood culture is the standard method and takes around two to five days in identifying the bacterial or fungal growth in blood culture [7]. If sepsis is suspected, other tests such as CBC, biochemical assays, and C-Reactive Protein (CRP) levels are conducted with blood culture. From a patient's haemogram, simple haematological parameters can be calculated easily [8]. An increasing number of studies have evaluated the association between RDW, MPV, NLR, and mortality rates or other complications in various disease states, such as heart failure and critical illness, trauma, and sepsis [9-11].

Higher mortality and morbidity levels in sepsis leads to an economic burden at both individual and community level. Mortality from sepsis remains unacceptably high, even after the many advances in antimicrobial agents and supportive care. Due to its varied etiologies and variable prognoses, sepsis patients are the most complex patients encountered in medical practice. To increase sepsis patient's quality of care, mortality prediction models utilizing available resources optimally need to be developed. In past decades many scoring models like Acute Physiology, Age and Chronic Health Evaluation (APACHE), Simplified Acute Physiology (SAPS), Mortality and Prediction Model (MPM), Multiple Organ Dysfunction (MOD), Open Data Inventory (ODIN), SOFA, Change Impact Score (CIS) etc have been developed to predict the outcome of admitted sepsis patients. The ICU resources are less in developing world and

utilisation of this scoring system results in timely management od sepsis patients [12].

Literature on diagnostic and early treatment of sepsis is majorly from developed countries. Research is still going on for the identification of markers to diagnose sepsis, severe sepsis, and septic shock. Extensive research to identify biomarkers for sepsis is needed from developing countries like India. Automated analysers are used to test CBC in most sepsis patients admitted to the emergency medical services. These automated analysers provide RDW, NLR, MPV which are routinely provided within the CBC. Inexpensive, routinely available, and rapidly measurable prognostic tools have clinical utility in the identification of a subset of patients with severe sepsis who need aggressive management. Therefore, the present study sought to evaluate the prognostic efficiency of RDW, the NLR, MPV in evaluating sepsis severity. The aim of this study was to compare the prognostic significance of RDW, MPV, NLR, and SOFA score with clinical outcome (survivors and non survivors) among sepsis patients.

MATERIALS AND METHODS

A prospective observational study was conducted for a period of 18 months from January 2018 to July 2019 in Department of General Medicine and ICU at tertiary care and research center in South India. Sepsis patients admitted to the General Medicine, and ICU department was considered the study population. Approval was obtained from the Institutional Ethical Committee of the concerned tertiary care setting. (Number-SDUMC/KLR/IEC/08/2017-18). All participants gave written informed consent. Confidentiality of the study subjects was maintained throughout.

Sample size calculation: The sample size was calculated assuming the expected Area Under Receiver Operating Curve (ROC) curve for the SOFA scoring system in predicting mortality as 0.78 as per Kim YC et al., the null hypothesis value of area under ROC curve was considered 0.5, the ratio of sample size is in the negative and positive group was considered as 1:2 [13]. The other parameters considered for the sample size calculation included a 5% alpha error and 99% study power. As per the calculation mentioned above, the required sample size was 66 as 44 were positive, and 22 were negative. To account for the non participation, rate/absence of about 20%, another 8 & 4 subjects were added to the sample, respectively. Hence, the final required sample size was 52 and 26 in each positive and negative groups. In the end, it was considered 79 and 41 subjects in positive and negative groups. Sample size calculation was done using coGuide software. For the feasibility of the study, all 120 subjects were selected according to the universal sampling method.

Inclusion criteria: Patients >18 years of age with sepsis (diagnosed as per "The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)" [4]. Sepsis should be defined as life threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%.

Exclusion criteria: Before infection, patients with pre-existing organ dysfunction (chronic kidney disease, decompensated liver disease, cardiac disease), patients with blood loss >10% blood volume, who had blood product transfusion in the week before admission were excluded from the study. In addition patients with haematological diseases such as anaemia, hypersplenism, haematological malignancy, metastatic bone marrow infiltration by malignancy, recovery after bone marrow hyperplasia, patients who had undergone recent chemotherapy and pregnant individuals were excluded from the study.

The parameters evaluated were: demographic data, co-morbidities, clinical findings at the time of admission, microorganism proliferation in the wound culture, laboratory findings (MPV, RDW, NLR), recorded at admission and within 24 hours after ICU admission.RDW to platelet count ratio (RPR) was also calculated. However, only RDW, MPV, NLR, and SOFA scores were assessed in the present study.

Study Procedure

Venous blood (3 mL) was collected from patients into an Ethylenediaminetetraacetic Acid (EDTA) containing tube and centrifuged at 3,000 rpm for 15 minutes, by automated CBC analyser "Cell Dyne Ruby" (Abbott, Diagnostic ®). The RDW, NLR, MPV values were obtained as part of the CBC results. RDW was calculated by dividing the standard deviation (SD) of the Mean Corpuscular Volume (MCV) and multiplying by 100, which is a percentage on behalf of the RBC size heterogeneity. NLR is calculated by dividing number of neutrophils with number of lymphocytes. Increased neutrophils and decreased lymphocytes count is seen during stress which is a physiological immune response of leucocytes. An objective parameter MPV is used to determine platelet size.

Simple and objective SOFA score measures individual or aggregate organ dysfunction in six organ systems (respiratory, coagulatory, liver, cardiovascular, renal, and neurologic). The parameters used to calculate the SOFA score are PaO_2/FiO_2, platelet count, bilirubin, blood pressure, inotropic agent, a Glasgow Coma Score Scale (GCS), and creatinine or urine output.

Normal function is scored 0 for patient without previously known co-morbidity like cirrhosis, chronic kidney disease. Score 4 was given for the most abnormal condition giving a possible score of 0 to 24 on each day of ICU stay. Maximal SOFA score is sum of the highest score per individual during the entire ICU stay. A higher SOFA score increases the probability of mortality. A SOFA score >15 predicts mortality of 90% [10,14,15]. The SOFA score was recorded at admission. All patients were followed-up at the hospital until discharge, death, or a maximum of 14 days. Data of patients requiring inotropic and ventilator support, renal replacement therapy for adverse events was recorded. Mortality was considered the primary outcome variable. Ventilator support, ionotropic support, renal replacement was considered as secondary outcome variables. SOFA score, RDW, NLR, and MPV levels were considered explanatory variables for sepsis patient's mortality.

STATISTICAL ANALYSIS

Mean and standard deviation was used to represent continuous data and frequencies and proportions for categorical data. To test the mean difference between two quantitative variables, an independent t-test was used and Chi-square test or Fischer's exact test was used for qualitative data. Correlations were performed with pearson correlation coefficient SOFA score, RDW, MPV, and NLR were further analysed using the ROC, and optimal cut-off points were chosen for the calculation of sensitivity, specificity. ROC of 0.5 predicts an outcome better than chance. An area under the ROC was a fairly good prediction when it was >0.8 p-value was set at ≤0.05. coGuide software, V.1. was used for data analysis [16].

RESULTS

All 120 subjects were sorted into two groups. Survivors group had 79 (65.8%) subjects, and 41 (34%) were in non-survivor's groups. Most of the survivors were in the age group 60-79 years 29 (36.71%). In contrast, non survivors fall into 40-59 years majorly with 41.46% (17 out of 41). No significant difference was seen with age between the study group (p>0.05). Most of the 41 (51.9%) participants were male among survivors and non survivors 27 (65.85%). Symptoms such as fever, cough, breathlessness, altered sensorium, vomiting, and abdominal pain between survivors and non survivors were insignificant [Table/Fig-1].

Parameters	Study group		p-value
	Survivors n (%)	Non survivors n (%)	
Age group (in years)			
20 to 39 years	11 (13.92%)	7 (17.07%)	0.424†
40 to 59 years	24 (30.38%)	17 (41.46%)	
60 to 79 years	29 (36.71%)	13 (31.71%)	
80 to 99 years	15 (18.99%)	4 (9.76%)	
Gender			
Male	41 (51.9%)	27 (65.85%)	0.143†
Female	38 (48.1%)	14 (34.15%)	
Symptoms			
Fever	62 (78.48%)	31 (75.61%)	0.721†
Headache	3 (3.8%)	0 (0%)	*
Cough	35 (44.3%)	19 (46.34%)	0.831†
Breathlessness	25 (31.65%)	18 (43.9%)	0.184†
Altered sensorium	21 (26.58%)	18 (43.9%)	0.055†
Vomiting	10 (12.66%)	3 (7.32%)	0.539‡
Decreased urine output	1 (1.27%)	0 (0%)	*
Abdominal pain	5 (6.33%)	5 (12.2%)	0.307‡

[Table/Fig-1]: Demographics, and clinical characteristics (n=120). Survivors (n=79), Non survivors (n=41).
*Due to 0 subjects in the cells, no statistical test was applied †chi-square test, ‡Fishers exact test p≤0.05 was significant. p≤0.001 was highly significant

Survivors and non survivors were commonly diagnosed with lower respiratory tract infections and lower respiratory tract infections with acute respiratory distress syndrome and the association was significant between groups (p<0.005) Urosepsis, acute gastroenteritis and other diagnosis, cultured organisms, and co-morbidities were not associated significantly between survivors and non survivors [Table/Fig-2].

Parameters	Study group		p-value
	Survivors n (%)	Non survivors n (%)	
Acute gastroenteritis	6 (7.59%)	1 (2.44%)	0.420*
Cellulitis	8 (10.13%)	0 (0%)	†
Lower respiratory tract infections	46 (58.23%)	15 (36.59%)	0.025‡
Acute respiratory distress syndrome	2 (2.53%)	13 (31.71%)	<0.001‡
Meningitis	7 (8.86%)	2 (4.88%)	0.717*
Neurological infection (encephalitis)	1 (1.27%)	0 (0%)	†
Urosepsis	9 (11.39%)	10 (24.39%)	0.064‡
Cultured organism			
No organism	65 (82.28%)	29 (70.73%)	0.145‡
Klebsiella pneumoniae	0 (0%)	1 (2.44%)	†
Acinetobacter species	3 (3.8%)	4 (9.76%)	0.229*
Acid-fast bacilli	1 (1.27%)	0 (0%)	†
Candida albicans	1 (1.27%)	0 (0%)	†
E.coli	7 (8.86%)	4 (9.76%)	1.000*
Klebsiella oxytoca	1 (1.27%)	0 (0%)	†
Klebsiella pneumonia Acinetobacter	1 (1.27%)	2 (4.88%)	0.269‡
Pseudomonas	0 (0%)	1 (2.44%)	†
Co-morbidities	69 (87.34%)	37 (90.24%)	0.770*

[Table/Fig-2]: Blood culture parameters and co-morbidities in study population (n=120).
*Fishers-exact test; †due to 0 subjects in the cells, no statistical test was applied; ‡chi-square test

Out of 79 survivors, 29 (36.71%) were on ventilator support, 42 (53.16%) were on inotropic support. Out of 41 non survivors, 40 (97.56%) had ventilator support, and 38 (92.68%) had inotropic support and the association was significant (p-value <0.001). The association was significant with respect to SOFA Score (p-value <0.001) Systolic Blood Pressure (SBP) (mm/hg), Diastolic Blood Pressure (DBP) (mm/hg), pulse (bpm), GCS and investigations like RDW, NLR and MPV (p-value <0.001). No significant difference was seen between the study group in RPR (p-value 0.784) [Table/Fig-3].

Parameters	Study group		p-value
	Survivors n (%)	Non survivors n (%)	
Diagnosis (Secondary outcome variables)			
Ventilator support	29 (36.71%)	40 (97.56%)	<0.001*
Inotropic support	42 (53.16%)	38 (92.68%)	<0.001*
Renal replacement therapy	10 (12.66%)	5 (12.2%)	0.942*
Sequential Organ Failure Assessment (SOFA)			
1-5	46 (58.23%)	10 (24.39%)	<0.001*
6-10	30 (37.97%)	16 (39.02%)	
11-15	3 (3.8%)	15 (36.59%)	
General examination (Mean and SD)			
Systolic blood pressure (SBP) (mm/hg)	109±32	91±19	<0.001†
Diastolic blood pressure (DBP) (mm/hg)	70±15	57±10	<0.001†
Pulse (bpm)	102±13	115±16	<0.001†
Glasgow coma scale	14±2	12±2	<0.001†
SOFA score	5±3	9±3	<0.001†
Investigations			
Red-Cell Distribution Width (RDW) (%)	14.37±0.62	16.20±0.81	<0.001†
Neutrophil Lymphocyte Ratio (NLR)	8.79±0.65	12.09±1.04	<0.001†
Mean Platelet Volume (MPV) (fl)	8.65±0.64	10.41±0.74	<0.001†
RPR	0.07 (0.05,0.14)	0.08 (0.03,0.17)	0.784‡

[Table/Fig-3]: Clinical and laboratory characteristics (n=120).
*Chi-square test; †Independent sample t-test; ‡Mann Whitney U test

A positive correlation was found between SOFA score and RDW (r=0.465; p<0.001), NLR (r=0.318; p<0.001), MPV (r=0.400; p<0.001) [Table/Fig-4].

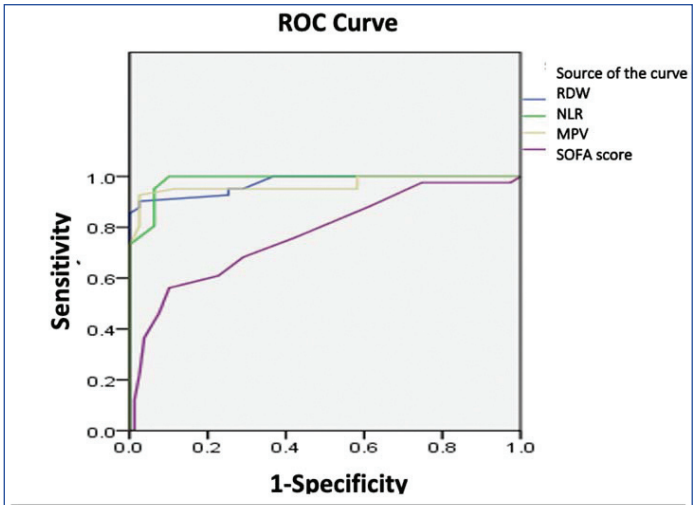
Parameters	Pearson correlation	p-value
RDW	0.465	<0.001**
NLR	0.318	<0.001**
MPV	0.400	<0.001**

[Table/Fig-4]: Correlation between SOFA score, RDW, NLR, MPV in the study population (N=120).

The calculated AUC for RDW was 0.973 with >15.2 as cut-off and 90.24% sensitivity, and 97.47% specificity. The yielded AUC for MPV was 0.966 with >9.4 as cut-off, and 92.68% sensitivity and 97.47% specificity. The AUC for NLR was 0.984 with >10.1 as cut-off and 100% sensitivity and 89.87% specificity. The predictive validity of SOFA, RDW, MPV, NLR in predicting survival (ROC analysis) was explained in [Table/Fig-5].

DISCUSSION

This prospective observational Study assessed prognostic importance of RDW, MPV and NLR among patients with sepsis, aiming to help clinicians in sepsis recognition and risk stratification. Most of the survivors were in the age group 60-79 years (36.71%), whereas most non survivors were in 40-59 years (41.46%). Most of the participants were males among survivors and non survivors. This finding was in comparison to a retrospective examination by Gozdas HT et al., in Turkey, where the mean age was 69.8±16.2, and 74 (61.2%) were male participants out of 121 [8]. In the present study, the SOFA score in non survivors was 9±3, which was more than survivors 5±3, and the association was significant. The finding was similar to a multicentric study by Lie KC et al., in Southeast Asia among 454 adult patients with community-acquired sepsis [17]. There was significantly higher total SOFA score during admission among non survivors than survivors (6.7 vs. 4.6, p<0.001**).



Parameter	SOFA score	RDW	NLR	MPV
Cut-off value	>8	>15.2	>10.1	>9.4
Sensitivity	56.10%	90.24%	100.00%	92.68%
Specificity	89.87%	97.47%	89.87%	97.47%

[Table/Fig-5]: Predictive validity of various scores in predicting survivor (ROC analysis). Predictive validity of SOFA score, RDW, NLR, and MPV

In the current study, RDW level was more in non survivors, 16.20±0.81, compared to survivors, 14.37±0.62, and the association was significant (p<0.001**). Krishna V et al., in South India, found higher levels of RDW in 30 (50%) out of 60 patients and a lesser levels of RDW in 30 (50%) patients and significant association was found between mortality and levels of RDW (p<0.05) [18]. Kim YC et al., in China reported RDW, platelet count, and delta neutrophil index as predictor for 28- day patient mortality [13]. The NLR value was more in non survivors 12.09±1.04 compared to survivors 8.79±0.65, and the association was significant (p<0.001**). The finding was similar to a cross-sectional study by Gupta A et al., in Jabalpur, India, among 117 patients with sepsis reported significant statistical difference in the mean and SD of NLR, RDW-SD, PLT, and Platelet Crit (PCT) on day one and day seven of observation [19]. Another ICU cross-sectional study by Pavan et al., in South India found the mean RDW was 14.455 and the mean NLR was 5.1645, and both parameters showed a significant correlation with SOFA score and outcome of sepsis patients [20]. Liu X et al., in China found NLR levels, independently associated with unfavorable clinical prognosis in patients with sepsis [21]. The MPV level was more in non survivors 10.41±0.74 compared to survivors 8.65±0.64 and the association was significant (p<0.001). This finding was in comparison to a prospective analysis by Orfanu A et al., in Romania, where MPV values increased to 8.1 (7.5; 8.7) in the sepsis group compared to controls [22].

The calculated AUC for RDW was 0.973 with >15.2 cut off and 90.24% sensitivity, and 97.47% specificity. Similarly Kim S et al., found AUC of 0.733 for each 1% increase in RDW, the AUC for MPV was 0.966 with >9.4 cut off, sensitivity was 92.68%, and specificity was 97.47% [23]. Similarly El-Said AM et al., in Egypt found a significant increase in levels of RDW and MPV and NLR (p<0.001) on admission and day three [5,24]. The AUC was 0.842, sensitivity was 89%, specificity was 85%, and 86% accuracy among septic shock patients. Another study by Varol E et al., found AUC for MPV as 0.65 and cut-off of 11.5 and AUC for NLR was 0.984 with >10.1 cut-off, 100% sensitivity and 89.87% specificity among unselected ICU patients [5,24]. Akili NB et al., found AUC of 0.61 with 11.9 cut-off similar to present study. Kaushik R et al., in India found AUC of 0.911, sensitivity was 87.5% and specificity was 90% almost similar to present study [25,26].

The definite pathophysiologic mechanism involving changes in MPV, NLR, RDW is still uncertain. It is believed that essential components in infection cascade, inflammation, oxidative stress, nutritional deficiencies, and renal dysfunction play an important role [27]. As per the study findings, there was an increase in the levels of RDW, MPV, NLR in sepsis patients. These blood parameters are quick and cost-effective that can be done even in resource stricken centers in India. The study's main strength was its prospective nature, and also the data which was obtained by real -time clinical parameters. This data can help health care professionals in saving crucial lives by monitoring and managing of severe sepsis patients and lowering mortality rate.

Limitation(s)

The study had few limitations. Patient's inflammatory status is dependent on CRP procalcitonin gamma-glutamyl transferase, etc. Levels of RDW, NLR, and MPV get affected by these inflammatory variables and as these were not explored in present study, Patient's inflammatory status cannot be made. The duration between blood sampling and measuring of RDW might affect RDW levels significantly. Intraday cell count variations should have been considered to further validate the findings. This was a single centre, prospective observational study with less sample size of 120, and these results cannot be generalised to overall population.

CONCLUSION(S)

This study demonstrated a strong correlation between increased levels of RDW, NLR, MPV and mortality among sepsis patients and can be used as prognostic markers for mortality prediction in adult sepsis patients. These markers showed good sensitivity, specificity and accuracy similar to other biomarkers. These markers are readily available from routine CBC test and can be evaluated quickly in less time and low cost. During early hospitalisation, these markers can be used as a specific index of haemogram in sepsis management. Further multicentric longitudinal studies with large samples are recommended to support the present study's findings.

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